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ARTICLE

Association of age-adjusted D-dimer with deep vein thrombosis risk in patients with spinal cord injury: a cross-sectional study

Jinlong Zhang[1,2] · Yunyun Fang[3] · Haiyun Pang[2] · Ye Tao[2] · Jing Zhou[2] · Shanshan Zhu[2] · Cheng Wang[2]

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Abstract

Study design Article.

Objective To elucidate the association of age-adjusted D-dimer (AAD) with deep vein thrombosis (DVT) risk to lower limbs in patients with spinal cord injury (SCI).

Setting Rehabilitation Medicine Department of the First Affiliated Hospital of China University of Science and Technology.

Methods Retrospective analysis of 250 patients with SCI in the rehabilitation department from August 2018 to December 2021. Quartiles divided the D-dimer level into four groups to analyze the association between AAD level and DVT risk.

Results Age was identified as a covariate of D-dimer and DVT risk. For non-adjusted model, when D-dimer increased by 1 mg/L, DVT risk increased 0.23-fold ($P < 0.05$); for minimally-adjusted model (adjusted for age), the risk increased 0.22-fold ($P < 0.05$); and for fully-adjusted model (adjusted for age, sex, pulmonary infection, degree, grades, and career), it increased 0.19-fold ($P < 0.05$). AAD had a curvilinear association with DVT risk, and the fold point was 1.9 mg/L ($P < 0.05$). When serum AAD level was <1.9 mg/L (K < 1.9), the estimated change in DVT risk was 3.34 ($P < 0.05$), and when serum AAD level was >1.9 mg/L (K > 1.9), the estimated change was 1.14 ($P < 0.05$). Urinary tract infection (UTI) and fibrinogen(tertile) had a interaction association with D-dimer level and DVT risk (P interaction < 0.05).

Conclusion Patients with SCI who receive rehabilitation treatment with AAD level >1.9 mg/L need to be paid close attention to, especially those with UTI and high levels of fibrinogen.

Introduction

Deep vein thrombosis (DVT) is a common complication among patients with spinal cord injury (SCI) [1]. A study found that D-dimer level was higher (≥10 μg/mL) in 15 (21.4%) out of 70 patients with SCI, and 9 (12.9%) out of these 15 were asymptomatic patients with venous thromboembolism (VTE) [2]. VTE incidence for patients with acute cervical SCI was reported to be 19.3%, and the researchers suggested that if ultrasound examination revealed DVT formation or D-dimer level increased to ≥10 μg/mL, the patient should undergo contrast examination to detect VTE, including DVT or pulmonary embolism [3]. A serum D-dimer level >10 μg/mL is a high-risk threshold for DVT in patients with SCI. After SCI, the blood flow rate in the veins slows down due to varying degrees of paralysis of the limbs and decreased muscle pumping function, and, thus, the blood is prone to hypercoagulation; as a result, it is the academic consensus that SCI leads to increased serum D-dimer levels [4–7]. For patients with SCI suspected of having DVT, if the

These authors contributed equally: Jinlong Zhang, Yunyun Fang

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✉ Cheng Wang
wcahslyy@163.com

[1] Rehabilitation Department, Hefei BOE Hospital of BOE Technology Group, Hefei, Anhui Province, People's Republic of China

[2] Rehabilitation Department, First Affiliated Hospital of University of Science and Technology of China (Anhui Provincial Hospital), Hefei, Anhui Province, People's Republic of China

[3] Traditional Chinese Medicine Department, Jiangning Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, People's Republic of China

combined application of B-ultrasound and serum examination determines that the D-dimer level is <1000 ng/mL, the probability of the patient not having DVT is 96.9% and the specificity is 66.9% [8]. The D-dimer level mainly reflects the fibrinolytic function and has certain predictive values for DVT formation [9, 10].

After adjusting for age, serum D-dimer level can improve the diagnosis of DVT [10]; age-adjusted D-dimer (AAD) cutoff value not only showed higher specificity than the existing D-dimer value (24.6% vs. 8.5%) but also had a higher negative predictive value (91.8% vs. 89.7%); thus, the researchers concluded that DVT can be ruled out using AAD levels [11]. Compared to the conventional D-dimer, the AAD performed better in DVT screening, which was clinically useful [12]. However, another study found that changing the laboratory-reported D-dimer reference interval for pulmonary embolism (PE) evaluation was not associated with a decrease in advanced chest imaging, such as computed tomography pulmonary angiography, and there was a significant difference in the AAD reference interval in the post-intervention period [13].

However, for patients with SCI hospitalized in the Department of Rehabilitation Medicine for treatment, the relationship between serum AAD level and the DVT risk in the lower limbs is yet to be fully elucidated. The present study was aimed at understanding the association between AAD and the DVT risk for SCI, which has a great value for the screening and diagnosis of DVT.

Methods

Data collection and flow chart of the study

Patient data were obtained for 262 patients with SCI hospitalized in the Rehabilitation Medicine Department of the First Affiliated Hospital of China University of Science and Technology from August 1, 2018, to December 31, 2020. Nine patients with SCI were excluded due to cause of SCI were not clear and lack of lower-limb Doppler ultrasound examination findings. Another three cases were excluded because degree and American Spinal Cord Injury Association (ASIA) grades were not assessed. Finally, 250 (95.42%) patients were included, of whom 86 (34.40%) had lower-extremity DVT during hospitalization in the rehabilitation department (Fig. 1).

Statistical methods

The mean (standard deviation) [Mean (SD)] and median (minimum−maximum) [Median (Min−Max)] are expressed for continuous variables. Number of cases (*N*, *N*%), odds ratio (OR), and 95% confidence interval (CI) are expressed for categorical variables. Univariate and multivariate binary logistic regression model were used to analysis the association between D-dimer level and DVT risk with three distinct models. Model 1 was the non-adjusted model with no covariates adjusted. Potential confounders were selected if they changed the estimates of DVT risk by at least 10% in the final models [14, 15]. Model 2 was the minimally-adjusted model with age adjusted. Model 3 was the fully-adjusted model with the confounders, demographic factors (sex and age) and unbalanced probable variables (presented in Table 2 adjusted). Threshold saturation effect analysis, Student's *t*-test, Mann–Whitney *U* rank-sum test, and Pearson's chi-square tests were used to analyze the data. We used the generalized additive model (GAM) and smooth curve fitting (penalized spline method) to address the nonlinearity between D-dimer and DVT risk. The fold point was first computed using a recursive algorithm when nonlinearities were detected, and then a two-piece binary logistic regression model was constructed on either side of the fold point. Subgroup analysis was performed using a stratified binary logistic regression model. For D-dimer level, we first converted it to categorical variables according to fourth quartile (Quartile, Q1–4 group), and then performed an interaction analysis. To modify the effect on the subgroup indicator was followed by a test for the likelihood ratio. In addition, we also conducted a sensitivity analysis to analyze the robustness of the results. To validate the results of D-dimer as a continuous variable and investigate the likelihood of nonlinearity, D-dimer was transformed into a categorical variable according to the fourth quartile(Quartile, Q1–4 group). A generalized estimated equation model was applied for multivariable logistic regression analysis as a covariate screening test. A two-sided $P < 0.05$ was indicated as statistically significant. All analyses were performed using R statistical package (R Foundation; http://www.r-project.org; version 3.4.3) and EmpowerStats (www.empowerstats.com; X&Y Solutions Inc.).

Results

Characteristics of study population

Based on the serum D-dimer level, a four-class grouping was performed, with 62 cases in the Q1 and Q2 groups and 63 cases in the Q3 and Q4 groups. The age, D-dimer level, rate of trauma, degree of complete injury, pulmonary infection, and DVT risk were highest in Q4 group, followed by followed by Q3, Q2, and Q1 groups ($P < 0.05$). The ASIA-A grades, urinary tract infection and the proportion of patients with SCI who were farmer were higher in Q4 group, followed by Q2, Q3, and Q1 groups

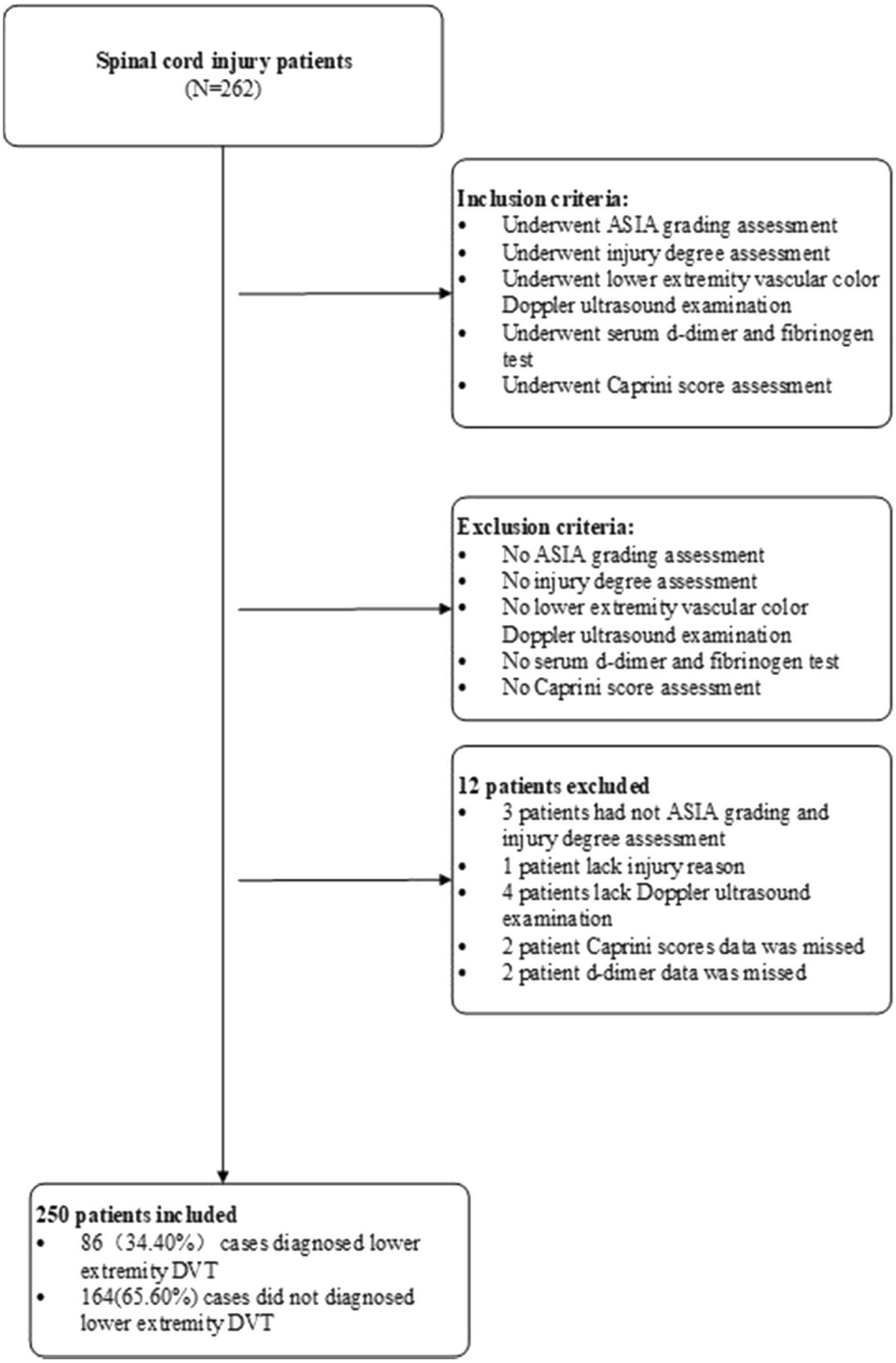

Fig. 1 Flow chart of the study. Inclusion and exclusion criteria are as follows. ASIA American Spinal Cord Injury Association, DVT deep vein thromobosis.

($P < 0.05$). Serum fibrinogen levels in the patients were the highest in Q3 group, followed by Q4, Q2, and Q1 groups ($P < 0.05$). TThe rate of patients with SCI with neck was the highest in Q3 group, followed by Q2, Q4, and Q1 groups ($P < 0.05$). There was no significant difference in sex and smoking history ratio among the four groups ($P > 0.05$; Table 1).

Univariate logistic regression analysis of D-dimer level and DVT risk

Univariate logistic regression analysis found that if age increased by 1 year, the DVT risk increased 0.06-fold among patients with SCI ($P < 0.05$). For every increase of 1 mg/L of the D-dimer level, the DVT risk increased

Table 1 Characteristics of the study population.

Quartered subgroup	Q1	Q2	Q3	Q4	*P*-value
Mean(SD) Median(Min−Max)/*N*(*N*%)					
N	62	62	63	63	
Age(years)	43.65 (16.16) 44.00 (15.00–75.00)	48.82 (13.88) 50.00 (13.00–74.00)	51.54 (16.35) 52.00 (15.00–85.00)	52.95 (12.60) 53.00 (21.00–79.00)	0.003*
D-dimer(mg/L)	0.31 (0.13) 0.32 (0.00–0.48)	0.94 (0.33) 0.86 (0.50–1.49)	2.25 (0.57) 2.08 (1.50–3.55)	9.22 (4.97) 7.80 (3.56–23.64)	<0.001*
Fibrinogen(g/L)	2.81 (1.05) 2.81 (0.00–5.48)	3.89 (1.31) 3.60 (2.08–7.67)	4.50 (1.70) 4.58 (0.91–12.20)	4.34 (1.39) 3.98 (2.02–7.63)	<0.001*
Sex					0.988
Male	46 (74.19%)	47 (75.81%)	47 (74.60%)	46 (73.02%)	
Female	16 (25.81%)	15 (24.19%)	16 (25.40%)	17 (26.98%)	
Reasons					0.004*
Traumatic	44 (70.97%)	47 (75.81%)	49 (77.78%)	60 (95.24%)	
Non-traumatic	18 (29.03%)	15 (24.19%)	14 (22.22%)	3 (4.76%)	
Pulmonary infection					0.004*
No	57 (91.94%)	53 (85.48%)	47 (74.60%)	43 (68.25%)	
Yes	5 (8.06%)	9 (14.52%)	16 (25.40%)	20 (31.75%)	
Urinary tract infection					<0.001*
No	43 (69.35%)	27 (43.55%)	29 (46.03%)	17 (26.98%)	
Yes	19 (30.65%)	35 (56.45%)	34 (53.97%)	46 (73.02%)	
Injury parts					0.018*
Neck	28 (45.16%)	35 (56.45%)	44 (69.84%)	29 (46.03%)	
Non-neck	34 (54.84%)	27 (43.55%)	19 (30.16%)	34 (53.97%)	
Degree					0.001*
	51 (82.26%)	46 (74.19%)	44 (69.84%)	32 (50.79%)	
Incompleteness					
Completeness	11 (17.74%)	16 (25.81%)	19 (30.16%)	31 (49.21%)	
Grades					0.029*
ASIA-A	10 (16.13%)	14 (22.58%)	11 (17.46%)	26 (41.27%)	
ASIA-B	10 (16.13%)	12 (19.35%)	12 (19.05%)	10 (15.87%)	
ASIA-C	12 (19.35%)	13 (20.97%)	19 (30.16%)	12 (19.05%)	
ASIA-D	30 (48.39%)	23 (37.10%)	21 (33.33%)	15 (23.81%)	
Career					0.026*
Non-farmer	44 (70.97%)	35 (56.45%)	43 (68.25%)	30 (47.62%)	
Farmer	18 (29.03%)	27 (43.55%)	20 (31.75%)	33 (52.38%)	
Smoking history					0.143
No	53 (85.48%)	50 (80.65%)	54 (85.71%)	45 (71.43%)	
Yes	9 (14.52%)	12 (19.35%)	9 (14.29%)	18 (28.57%)	
DVT					<0.001*
DVT-NO	55 (88.71%)	52 (83.87%)	35 (55.56%)	22 (34.92%)	
DVT-YES	7 (11.29%)	10 (16.13%)	28 (44.44%)	41 (65.08%)	

*$P < 0.05$.

0.23-fold ($P < 0.05$). The DVT risk increased 1.35-fold among patients with SCI with pulmonary infection compared to those without pulmonary infection ($P < 0.05$) and increased 0.69-fold for patients with complete SCI compared to those with incomplete SCI ($P < 0.05$). The DVT risk in ASIA-D decreased 0.95-fold compared to that in ASIA-A ($P < 0.05$). Furthermore, the DVT risk increased 0.68-fold in patients with SCI who were farmers compared

Table 2 Univariate logistic regression analysis of D-dimer level and DVT risk.

Variables	Statistics Mean(SD) Median (Min−Max)/*N*(*N*%)	DVT incidence OR (95%CI)	*P*-value
Sex			
Male	186 (74.40%)	1.0	
Female	64 (25.60%)	−0.29 (−0.90–0.33)	0.358
Age(years)	49.26 (15.17) 50.50 (13.00–85.00)	0.06 (0.04–0.08)	<0.001*
D-dimer(mg/L)	3.20 (4.36) 1.50 (0.00–23.64)	0.23 (0.14–0.31)	<0.001*
Fibrinogen(g/L)	3.89 (1.53) 3.66 (0.00–12.20)	0.16 (−0.01 to 0.33)	0.067
Reasons			
Traumatic	200 (80.00%)	1.0	
Non-traumatic	50 (20.00%)	−0.37 (−1.05 to 0.31)	0.286
Pulmonary infection			
No	200 (80.00%)	1.0	
Yes	50 (20.00%)	1.35 (0.71–1.99)	<0.001*
Urinary tract infection			
No	116 (46.40%)	1.0	
Yes	134 (53.60%)	0.28 (−0.25 to 0.81)	0.298
Injury parts			
Neck	136 (54.40%)	1.0	
Non-neck	114 (45.60%)	−0.23 (−0.76 to 0.30)	0.390
Degree			
Incompleteness	173 (69.20%)	1.0	
Completeness	77 (30.80%)	0.69 (0.13–1.24)	0.015*
Grades			
ASIA-A	61 (24.40%)	1.0	
ASIA-B	44 (17.60%)	−0.70 (−1.53–0.12)	0.092
ASIA-C	56 (22.40%)	−0.20 (−0.93 to 0.54)	0.599
ASIA-D	89 (35.60%)	−0.95 (−1.65 to −0.25)	0.008*
Career			
Non-farmer	152 (60.80%)	1.0	
Farmer	98 (39.20%)	0.68 (0.15–1.22)	0.012*
Smoking history			
No	202 (80.80%)	1.0	
Yes	48 (19.20%)	0.39 (−0.26 to 1.03)	0.240
Quartered subgroup			
Q1	62 (24.80%)	1.0	
Q2	62 (24.80%)	0.41 (−0.62 to 1.45)	0.436
Q3	63 (25.20%)	1.84 (0.91–2.77)	0.001*
Q4	63 (25.20%)	2.68 (1.74–3.63)	<0.001*

*$P < 0.05$.

to those who were not ($P < 0.05$). An increase of 1 mg/L of the D-dimer level resulted in an increase in the DVT risk, which was 2.68-fold higher in Q4 group than in Q1 group ($P < 0.05$), 1.84-fold higher in Q3 group than in Q1 group ($P < 0.05$), and 0.41-fold higher in Q2 group than in Q1 group($P > 0.05$) (Table 2).

Multivariate binary logistic regression analysis of D-dimer level and DVT risk

Covariate screening test showed that age was a covariate of D-dimer and DVT risk. Multivariate regression analysis found that in the minimally-adjusted model (adjusted for age), for every increase of 1 mg/L of D-dimer level, the DVT risk increased 0.22-fold ($P < 0.05$); and in the fully-adjusted model (adjusted for age, sex, pulmonary infection, degree, grades, and career), it increased 0.19-fold ($P < 0.05$; Table 3 and Supplementary Table 1).

Curve line correlation between AAD level and DVT risk

After the covariate-age was adjusted, the AAD had a curvilinear association with DVT risk (Fig. 2). In order to further verify the association; we transformed the D-dimer level into Log10, and had a logarithmic linear growth association with DVT risk (Supplementary Fig 1).

Threshold saturation effect between AAD level and DVT risk

Threshold saturation effect analysis was performed between serum AAD level and DVT risk in patients with SCI. The logarithmic likelihood ratio test showed that AAD had a curvilinear association with DVT risk, and there was a fold point (K = 1.9 mg/L) ($P < 0.05$). When the AAD level was <1.9 mg/L (K < 1.9), the estimated change in DVT risk was 3.34 and 95% CI was 1.84–6.04. The mean DVT risk increased 234% with an increase of 1 mg/L in the AAD level when it was <1.9 mg/L, and the difference was statistically significant ($P < 0.05$). The mean DVT risk increased 11% with an increase of 1 mg/L in the AAD level when it was >1.9 mg/L, and the difference was also statistically significant ($P < 0.05$; Table 4).

Sensitive analysis of D-dimer level and DVT risk

Subgroup and interaction analysis were performed between serum D-dimer level and DVT risk in patients with SCI. The estimated change in DVT risk was >1 in different groups and the plot were at the right of reference, indicate the D-dimer level would be an independent risk factor for DVT ($P < 0.05$). In non-traumatic reason and ASIA-C grades of SCI, the 95%CI crossed with reference line ($P < 0.05$), however, the estimated change was still >1 (Fig. 3).

Interaction screening analysis showed urinary tract infection (UTI) and fibrinogen tertile had an interaction

Table 3 Multivariate logistic regression analysis of D-dimer level and DVT risk.

Exposure	Non-adjusted OR (95%CI)	*P-value*	Minimally-adjusted OR (95%CI)	*P*-value	Fully-adjusted OR (95%CI)	*P*-value
D-dimer(mg/L)	0.23 (0.14, 0.31)	<0.001*	0.22 (0.13, 0.30)	<0.001*	0.19 (0.09, 0.28)	<0.001*
Quartered subgroup						
Q1	1.0		1.0			
Q2	0.41 (−0.62, 1.45)	0.436	0.24 (−0.84, 1.33)	0.659	0.02 (−1.09, 1.14)	0.966
Q3	1.84 (0.91–2.77)	0.001*	1.65 (0.66, 2.63)	0.001*	1.49 (0.48, 2.51)	0.004*
Q4	2.68 (1.74–3.63)	<0.001*	2.55 (1.55, 3.55)	<0.001*	2.23 (1.20, 3.26)	<0.001*

Minimally-adjusted, adjusted for age; Fully-adjusted, adjusted for age, sex, pulmonary infection, degree, grades, and career.

*$P < 0.05$.

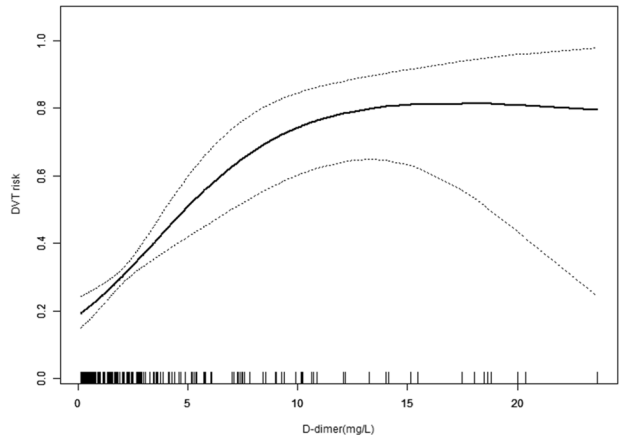

Fig. 2 Graph depicting the association between AAD level and DVT risk. The black continual line is a fitting line of AAD and DVT risk, and the interval between the black dot lines is the 95%CI.

Table 4 Analysis of threshold saturation effect between AAD and DVT risk.

Outcome	DVT incidence OR (95%CI) *P*-value	
Model I		
Linear regression coefficient	1.24 (1.14–1.36)	<0.001*
Model II		
Fold point(K) of D-dimer	1.9	
<K regression coefficient 1	3.35 (1.85–6.07)	<0.001*
>K regression coefficient 2	1.12 (1.02–1.23)	0.023*
Logarithmic likelihood ratio test		<0.001*

*$P < 0.05$.

association with D-dimer level and DVT risk (*P* interaction <0.05; Supplementary Table 2). Adjusted the confounders (Model I: age), meanwhile we adjusted demographic factors and unbalanced probable variables (Model II: sex, age, pulmonary infection, degree, grades, and career; presented in Table 2), fibrinogen(tertile) and UTI were still the effect modifier (*P* interaction <0.05; Supplementary Tables 3, 4).

Discussion

In our study, 86 (34.40%) patients with SCI had lower-extremity DVT during hospitalization in the rehabilitation department. Moreover, our study found that age was related to the DVT risk and that age was a synergy variable between D-dimer and DVT risk. After adjusting the covariate of age, a curvilinear relationship was noted between the ADD level and DVT risk, and there was a fold point. Fibrinogen (tertile) and UTI were the effect modifier of D-dimer level and DVT risk.

The incidence of total DVT ranges from 50 to 100% in untreated patients, and PE was the third most common cause of mortality in these patients [16]. A total of 14 patients with SCI (31%) were diagnosed with DVT using duplex ultrasonography [17]. D-dimer assays vary widely depending on the antibody used, capture method, instrumentation required, and calibration standards [18]. Although D-dimer can improve the diagnostic efficiency of DVT [19], in clinical settings, misdiagnosis caused by other factors should be considered. However, another study concluded that the application of an AAD threshold in patients with suspected PE increased the number of patients in whom imaging can be withheld [20].

The National Institute for Health and Care Excellence recently recommended the use of AAD for VTE investigations to help reduce the burden of diagnostic imaging in over-extended radiology [21, 22]. In India, higher age and quadriplegia were found to be the only factors that could be correlated to DVT and PE following SCI [23]. Moreover, a study found that both traditional D-dimer and AAD were associated with a high and similar negative predictive value and similar utility in the diagnosis of DVT [24]. However, another study found that the AAD cutoff level was not useful in the diagnostic algorithm of DVT in an ambulatory

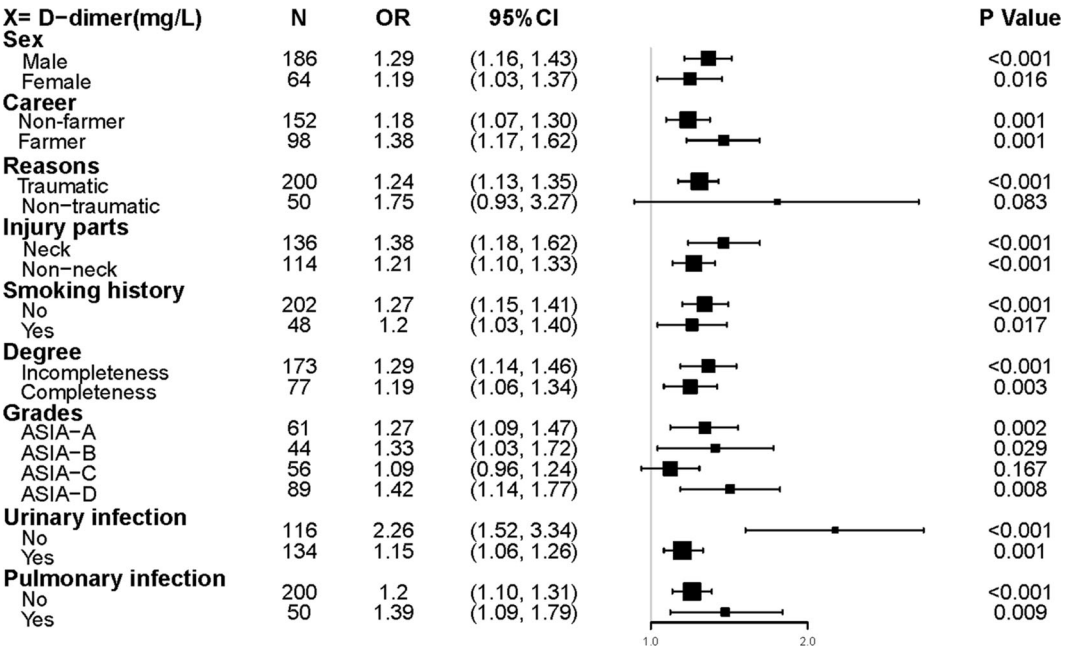

Fig. 3 Subgroup analyses on D-dimer of DVT risk. The back square indicates OR value. The perpendicular line is a reference line and the horizontal line indicates 95%CI.

care setting [25]. To the best of our knowledge, there is no specific research on the traditional D-dimer or AAD level of the effect value of DVT risk for patients with SCI in a rehabilitation department, which is disadvantageous to the prevention of DVT in these patients. In order to reflect the overall picture of clinical research more objectively and comprehensively and to reflect the real-world clinical research, not only age but also other variables with significant differences in baseline data were adjusted in this study; the D-dimer level still remained associated with DVT risk among the patients with SCI and was very similar to that in the non-adjusted model.

A study found that the incidence of DVT in patients with SCI was 100% detected by the 125I-labeled fibrinogen test and confirmed by contrast venography [26], and 125I fibrinogen lower limbs scanning was a more sensitive indicator of DVT events than impedance venography or plethysmography [27]. Neurogenic bladder disorders are common among patients with SCI, which can result in UTI [28]. A study reported a patient with DVT and PE secondary to neurogenic bladder [29], another study reported a patient with DVT caused by compression on the right iliac vein by a distend bladder [30]. Our study also found that fibrinogen and UTI were the effect modifier of D-dimer level and DVT risk.

In this study, AAD had a curvilinear association with DVT risk, and the fold point was 1.9 mg/L ($P < 0.05$). The estimated change of DVT risk was higher for AAD levels <1.9 mg/L than for those >1.9 mg/L (3.34 vs. 1.14). Therefore, more attention should be paid to patients with SCI, especially those whose AAD levels are <1.9 mg/L. Moreover, patients with SCI having increased D-dimer levels should be suggested to undergo DVT preventive measures, including rehabilitation and anticoagulant treatments, and especially should pay more attention to those with UTI and higher serum fibrinogen level. Our research results may be valuable as reference for other researchers to conduct clinical randomized controlled studies in the future.

This study has some limitations. First, it did not conduct PE evaluations; only Doppler ultrasound was used to examine lower-extremity DVT. Second, this study had a cross-sectional design without follow-up, which thereby cannot explain the causal relationship between D-dimer and DVT, nor can it predict long-term DVT risk. It only describes an association between D-dimer and lower-extremity DVT risk during rehabilitation for patients with SCI. Third, this is a single-center study, and the application of research conclusions to other centers may not be accurate. Fourth, this research was conducted as a retrospective cross-sectional study; although our study found the fibrinogen and urinary tract infection had a interaction association for the association of D-dimer level and DVT risk, we can't conclude a longitudinal cohort reason between them, further higher quality studies should be conducted in the future, such as random control trials or cohort studies. Finally, this study could not observe the impact of uncollected variables on D-dimer and DVT risk, and there may

also be other covariates that affect the relationship between AAD and DVT risk.

Conclusion

Patients with SCI who receive rehabilitation treatment with D-dimer level >1.9 mg/L need to be paid close attention to, especially those with UTI and high levels of fibrinogen.

Data and materials availability

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions JLZ: Conducted the study and wrote the draft. YYF: Designed the study, interpreted the data, and edited the manuscript. HYP, YT, JZ, and SSZ: Collected the data. CW: Planned the project, created and statistical analyzed the data. The authors all read and approved the final manuscript

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Ethics approval and consent to participate Informed consent was waived due to the nature of the retrospective study for participants, which coincident with ethical requirements and waiver from the ethics committee, the study approved by Ethics Committee of First Affiliated Hospital of the University of Science and Technology of China (Anhui Provincial Hospital), the approved number was 2020-RE-008.

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